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A. P. Fishman, … , F. Williams, A. Ellis

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**Research Article**



# MECHANISMS OF EDEMA FORMATION IN CHRONIC EXPERIMENTAL PERICARDITIS WITH EFFUSION [1]

By A. P. FISHMAN,[2] J. STAMLER,[3] L. N. KATZ, A. J. MILLER, E. N. SILBER, AND L. RUBENSTEIN
WITH THE TECHNICAL ASSISTANCE OF F. WILLIAMS AND A. ELLIS

*(From the Cardiovascular Department,[4] Medical Research Institute, Michael Reese Hospital, Chicago)*

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Recent studies of the mechanism of congestive heart failure have brought forth new data on the changes in cardiac output, central venous pressure, renal blood flow, and salt and water excretion, which have led to new interpretations of the pathogenesis of this syndrome (1–10). Several basic problems remain unsolved, however. Their resolution has been handicapped by the inability to reproduce chronic congestive heart failure in laboratory animals (11).

Chronic pericarditis with effusion resembles congestive heart failure in that both may exhibit congestion, fluid retention, edema and anasarca. We have recently produced chronic pericarditis with effusion in the dog by the introduction of irritative cellophane into the pericardial sac (12). Animals so treated eventually exhibited a syndrome of circulatory failure (insufficiency) with congestion. This experimental approach therefore provides a means for the investigation of the alterations in cardiodynamics and in renal function which lead to fluid accumulation. The changes observed in chronic experimental pericarditis with effusion have been analyzed in an attempt to explain the pathogenesis of fluid retention in this syndrome. This information is of value in attempting to elucidate the mechanisms of edema formation in chronic congestive heart failure.

## METHODS

*The production of pericarditis:* [5] An irritative cellophane was used to produce pericarditis with effusion.[6] Following anesthetization with intravenous sodium pentobarbital, the chest was entered through the fifth interspace. The parietal pericardium was incised and a bag of sterilized irritative cellophane was slipped over the heart, using a tension suture through the cardiac apex as a guide. Interrupted sutures fixed the bag to the parietal pericardium. The pericardium was then closed so that the bag was between it and the epicardium.

*Cardiac output determination:* Cardiac output determination by the Fick principle was initially attempted in anesthetized animals using methods previously described (16). However, the dogs with pericarditis died suddenly during administration of very small intravenous doses of pentobarbital for anesthesia. Hence all cardiac output determinations were subsequently made in unanesthetized animals, using a modification of Marshall's method (17). Essentially, the procedure involved obtaining mixed venous blood samples by direct right ventricular puncture with the dog on its left side. In this position, as determined by autopsy and angiocardiography, the dog's right ventricle was superficial. Arterial blood was obtained from the femoral artery or left ventricle. The latter was entered either through the septum or by direct puncture. Since the dog was kept in a comfortable position without manipulation, this procedure helped to maintain a resting state. Blood oxygen concentrations were determined in duplicate by the method of Van Slyke and Neill (18). Oxygen consumption was recorded using a modified Blalock mask (19) and clinical spirometer.

*Other techniques:* Unless otherwise indicated, all studies were done on trained unanesthetized male mongrel dogs in the post-absorptive state. Renal hemodynamics

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[5] Presented in part at the American Physiological Society Meetings, Detroit, Michigan, April, 1949 (12).
[6] Reports differ concerning the effect of cellophane on tissues (13, 14). Recently an irritative factor has been chemically identified in specific cellophanes (15). Apparently, ordinary commercial cellophane is physiologically inert. In the preparation of polythene cellophane, up to 1% dicetyl phosphate is added during the final processing. This alcohol and water insoluble adulterant is capable of stimulating an intense inflammatory reaction, and renders polythene cellophane irritative. This specific cellophane became for our purpose the vehicle for application of dicetyl phosphate to the visceral and parietal pericardial surfaces. Polythene cellophane 1.5 mil. containing dicetyl phosphate was supplied through the courtesy of Messrs. A. S. Taylor and C. L. Blair of the Technical Service Laboratory, Cellophane Division, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

were investigated using established clearance methods (20), as previously described (21). Effective renal plasma flow was measured by the para-aminohippurate (PAH) clearance (22) and glomerular filtration rate by the creatinine clearance (20). Osmotic diuresis was accomplished with 2.5% mannitol in distilled water, except when sodium clearance studies were done. Then either isotonic (0.9%) or hypertonic (2.5% or 5%) saline was used. Sodium clearances were calculated from plasma sodium levels, glomerular filtration rates and urinary sodium excretion rates (23). Plasma and urine sodium concentrations were determined by the methods of Bradbury (24) and Butler and Tuthill (25), respectively.

Plasma volume and thiocyanate space were determined by a modification of the method of Gregersen and Stewart (26). Plasma total protein concentration was determined by the method of Wolfson and his associates (27). The Wintrobe method was used for hematocrit determinations (28).

The peripheral venous pressure was recorded with a saline manometer from the left foreleg vein, with the dog on its right side. Zero level was taken at a point 5 cm. below the upper level of the thoracic cage. Intra-abdominal venous pressure was recorded via a No. 9 cardiac catheter connected to a saline or Hamilton manometer. Arterial pressure and heart rate were measured by direct arterial puncture and optical recording using a Hamilton manometer (29).

After operation, the presence of pericardial, pleural and abdominal fluid was determined by physical examination, fluoroscopy and needle puncture.

Pericarditis with effusion was produced in 15 dogs.[7] Of these, six were used in preliminary work verifying the method. Cardio-renal dynamic studies were done on the other nine animals. In three of these (P2, P4, P5) detailed data were sequentially obtained up to the time of natural exitus. Z102, P3 and P6 were similarly followed until death occurred during a laboratory procedure. Data on cardiac output after pericarditis induction is lacking for these dogs. Sodium clearances were studied in three animals (P4, P6, P7). Three dogs (P7, P8, P9) were used to study central and renal venous pressures.

## RESULTS

### 1. *Control data.*

Control data for cardiac output, renal clearances, peripheral venous pressure, plasma volume, thiocyanate space, hematocrit, plasma total protein and weight are summarized in Table I. In

[7] In a 16th dog, a non-irritative cellophane bag was inadvertently placed about the heart. Sequential studies in this animal (P1) revealed no physiological alterations over the course of three weeks. The dog was then sacrificed. There were no significant abnormal findings at necropsy.

TABLE I

*Average control data*

| Dog No. | Weight | S.A.* | Plasma proteins | Hematocrit | Plasma volume | SCN* space | GFR* | RPF* | RBF* | FF* | A-V* | C.I.* | V.P.* | Renal fraction* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *kg.* | $M^2$ | *gms. %* | *%* | *cc./$M^2$* | *cc./$M^2$* | *cc./min./$M^2$* | *cc./min./$M^2$* | *cc./min./$M^2$* | *%* | *vols. %* | *L/min./$M^2$* | *cm.$H_2O$* | *%* |
| P2 | 23.4 | .915 | 5.8 | 41 | 1370 | 7580 | 84 | 356 | 604 | 24.2 | 5.9 | 3.95 | 4 | 15.3 |
| P4 | 14.1 | .656 | 8.0 | 44 | 1530 | 7130 | 111 | 425 | 759 | 26.2 | 3.9 | 3.83 | 3 | 19.9 |
| P5 | 21.9 | .880 | 7.4 | 44 | 1482 | 7490 | 64 | 268 | 480 | 23.7 | 3.6 | 4.09 | 6 | 11.7 |
| Z102 | 15.2 | .684 | 7.0 | 47 | 1695 | 5670 | 105 | 297 | 560 | 32.0 | (3.4)† | (3.38)† | 4 | — |
| P3 | 15.8 | .707 | 7.5 | 45 | 1250 | 7400 | 82 | 318 | 578 | 25.8 | (2.5)† | (3.99)† | 5 | — |
| P6 | 17.5 | .754 | 6.9 | 47 | 1420 | 6320 | 110 | 396 | 746 | 27.8 | — | — | 8 | — |
| P1 | 18.9 | .798 | 7.9 | 37 | 1626 | 8500 | 104 | 424 | 672 | 24.5 | 3.9 | 4.05 | 6 | 16.7 |
| Mean | 18.1 | .777 | 7.2 | 44 | 1482 | 7156 | 94 | 355 | 628 | 26.5 | 4.3‡ | 3.98‡ | 5 | 15.8 |
| Range | 15.2–23.4 | .684–.915 | 5.8–8.1 | 37–47 | 1250–1695 | 5670–8500 | 64–111 | 268–425 | 480–759 | 23.7–32.0 | 3.6–5.9‡ | 3.83–4.05‡ | 3–8 | 11.7–19.9 |

* S.A. is the surface area calculated from the formula: $\frac{11.2\ W^{.667}}{10{,}000}$, where W is the weight in grams.

SCN is thiocyanate.
GFR is glomerular filtration rate.
RPF is renal plasma flow.

RBF is renal blood flow, calculated from the formula: $\frac{RPF}{1\text{-hematocrit}}$; hematocrits used were those obtained on clearance bloods.

FF is filtration fraction.
A-V is arteriovenous oxygen difference.
C.I. is cardiac index, or cardiac output per $M^2$.
V.P. is venous pressure.

Renal fraction is calculated from the formula: $\frac{RBF}{C.O.}$.

† Anesthetized determination.
‡ For unanesthetized determinations only.

TABLE II

*Preoperative and postoperative data, pericarditis with effusion*
*Dog P2*

| Date | Weight | Plasma proteins | Hemato-crit | Plasma vol. | SCN space* | GFR* | RPF* | FF* | Resp.* | $O_2$ cons.* | A-V* | C.O.* | V.P.* | B.P.* | P.P.* | H.R.* | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *kg.* | *gms. %* | *%* | *cc.* | *cc.* | *cc./min.* | *cc./min.* | *%* | *per min.* | *cc./min.* | *vols. %* | *L/min.* | *cm. $H_2O$* | *mm. Hg* | *mm. Hg* | *beats/min.* | |
| 4–19–49 | | | | | | 74 | 409 | 17.9 | 14 | | | | | | | | |
| 4–28 | 22.5 | 5.8 | 44 | 1136 | 7360 | | | | 14 | (85)† | (3.3)† | (2.57)† | | | | 136 | |
| 5–4 | 22.5 | 5.6 | 40 | | | 68 | 304 | 22.3 | | | | | 4,4‡ | 190/80 | 110 | 78 | |
| 5–5 | 22.0 | | | | | | | | 16 | (60)† | (2.2)† | (2.73)† | 4 | | | 124 | |
| 5–16 | 22.5 | 5.4 | 40 | 1360 | 6160 | | | | | | | | | 215/100 | 115 | | |
| 5–18 | 22.8 | 6.5 | 41 | | | 86 | 277 | 31.4 | | | | § | | 225/95 | 130 | | |
| 5–23 | 24.6 | | | | | | | | 12 | 213 | 5.9 | 3.61 | 3 | 150/75 | 75 | 108 | |
| 5–25 | 24.8 | | | | | | | | 19 | 275 | 5.6 | 4.91 | | 150/75 | 75 | 92 | |
| 5–26 | 25.0 | 5.4 | 41 | 1260 | 7270 | | | | 18 | 240 | 5.2 | 4.62 | 4 | 150/75 | 75 | 88 | |
| Mean | 23.4 | 5.8 | 41 | 1252 | 6943 | 77 | 326 | 24.2 | 16 | 243‖ | 5.6‖ | 4.34¶ | 4 | 150/75 | 75 | 86 | Mean B.P., P.P., and H.R. for period when dog was trained. |
| 6–7–49 | | | | | | | | | | Surgery | | | | | | | |
| 6–10 | 22.8 | 5.8 | | 1432 | 6600 | | | | 17 | 145 | 4.3 | 3.37 | 7,12‡ | 125/90 | 35 | 120 | V.P. on 6–9, 6 cm. $H_2O$. |
| 6–11 | 23.4 | | 43 | | | 67 | 380 | 17.5 | | | | | 6,11‡ | | | | Pericardial fluid obtained on tap; none removed. |
| 6–15 | 23.1 | | 36 | | | 85 | 447 | 19.0 | | | | | 10,10‡ | 120/80 | 40 | 135 | Eating well and active up to this date; V.P. on 6–13 and 6–14, 8 and 9 cm. $H_2O$. |
| 6–17 | 23.6 | 5.2 | 31 | 1533 | 7825 | | | | 20 | 160 | 6.1 | 3.20** | 14 | 120/80 | 40 | 136 | Progressive weakness and anorexia, 6–15 to 6–17; moderate ascites. No significant rise in cardiac output during excitement and exertion. |
| 6–20 | | | | | | | | | 36 | | | | 14 | | | | Marked weakness, respiratory difficulty prior to tap. |
| | | | | | | | | | | Pericardial Aspiration | | | | | | | |
| 6–20 | | | | | | | | | 24 | | | | 8†† | | | | Respiratory difficulty relieved by removal of 150–200 cc. fluid; Resp. fell from 36 to 24; $O_2$ consumption did not change. |
| 6–21 | 22.7 | | 37 | | | 95 | 411 | 23.1 | | | | | 14,16‡ | 145/80 | 65 | | |
| 6–23 | 24.1 | 4.8 | 32 | 1833 | 8040 | 62 | 317 | 19.5 | 30 | 163 | 6.6 | 2.73 | 13 | 150/80 | 70 | 156 | Weakness, respiratory distress reestablished. |
| 6–25 | | | | | | | | | | | | | | 80/50 | 30 | >200 | Circulatory collapse has apparently supervened. |
| 6–27 | 23.4 | | | | | 27 | 88 | 30.7 | | | | | 15,16‡ | | | | |
| 6–28 | | | | | | | | | | Death | | | | | | | |

* For symbols see Table I.
Resp. is respiratory rate.
C.O. is cardiac output.
B.P. is arterial blood pressure.
H.R. is heart rate.
P.P. is pulse pressure.
$O_2$ cons. is oxygen consumption.
† Anesthetized determinations
‡ Venous pressure after infusion for renal clearance.
§ Cardiac output during excitement and exertion was 7.60.
‖ Average of unanesthetized determinations.
¶ Average of unanesthetized determinations; the lowest value, 3.61 L/min., was taken as the valid control level, and hence appears in Table I.
** Cardiac output during excitement and exertion was 3.25.
†† Venous pressure following pericardial tap.

TABLE III

*Preoperative and postoperative data, pericarditis with effusion*
*Dog P4*

| Date | Weight | Plasma proteins | Hemato-crit | Plasma vol. | SCN space* | GFR* | RPF* | FF* | Resp.* | $O_2$ cons.* | A-V* | C.O.* | V.P.* | B.P.* | P.P.* | H.R.* | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *kg.* | *gms. %* | *%* | *cc.* | *cc.* | *cc./min.* | *cc./min.* | *%* | *per min.* | *cc./min.* | *vols. %* | *L/min.* | *cm. $H_2O$* | *mm. Hg* | *mm. Hg* | *beats/min.* | |
| 6–22–49 | | 8.1 | | | | 78 | 265 | 29.4 | | | | ‡ | 4,3§ | 140/85 | 55 | | |
| 6–29 | | | | | | | | | 16 | 80 | 3.4 | 2.40 | 2 | 150/65 | 85 | 86 | |
| 7–5 | 14.1 | 8.1 | 42 | 1005 | 4840 | | | | 20 | 115 | 4.3 | 2.67 | 2 | 145/70 | 75 | 70 | |
| 7–7 | 14.1 | 7.8 | 46 | 1002 | 4520 | 67 | 292 | 22.9 | | | | | | 150/65 | 85 | | |
| Mean | 14.1 | 8.0 | 44 | 1004 | 4680 | 73 | 279 | 26.2 | 18 | 98 | 3.9 | 2.51 | 3 | 150/75 | 75 | 78 | Control renal venous pressure = 10 cm. $H_2O$. |
| 7–15 | | | | | | | | | Surgery | | | | | | | | |
| 7–16 | | 7.6 | | | | | | | | | | | 2 | 140/75 | 65 | 140 | |
| 7–18 | | | | | | | | | | | | | 14 | | | | |
| 7–19 | 14.1 | 7.6 | 42 | | | 75 | 277 | 27.0 | 32 | 118 | 4.5 | 2.40 | 13,13§ | 150/85 | 65 | 146 | |
| 7–22 | 14.5 | 7.6 | 48 | 978 | 5143 | | | | 37 | 110 | 3.6 | 3.06 | 12,18§ | | | 174 | Weakness, anorexia, ascites. |
| 7–25 | 14.5† | | 23 | | 4780† | 56 | 139 | 40.3 | 35 | 165 | 6.4 | 2.65 | 13,17§ | 120/70 | 50 | 156 | Marked ascites; great difficulty in obtaining diuresis (see text). Renal venous pressure = 21 cm. $H_2O$. |
| 7–26 | 17.7 | 6.6 | 21 | 1255 | 9010 | | | | 40 | | | | 17 | | | | Pulse thready, barely perceptible, could not be counted; blood pressure could not be recorded; animal obviously in pre-terminal circulatory collapse; death occurred later that day. Intrapericardial pressure immediately postmortem was 14 cm. $H_2O$. |

* For symbols see Tables I and II.

† This is weight and SCN space prior to saline infusion for sodium clearance study; weight after clearance was 17.7; as indicated by SCN space on 7–26, marked prolonged fluid retention occurred; see text.

‡ Cardiac output during excitement and exertion was 8.42.

§ Venous pressure after infusion for renal clearance.

general, these results are in agreement with values previously reported from this and other laboratories (16, 17, 21, 30–32).

2. *Morphological data.*

Each of the dogs showed similar findings, varying in degree. In brief, there was a massive serosanguinous pericardial effusion distending the pericardial sac and compressing the heart. The pericardium was thickened and rigid. The surface of the heart was dull and opaque with many fibrinous and fibrous strands. The surface markings of the heart were completely obliterated; the coronary vessels and auriculoventricular groove could not be identified.

Ascites, hydrothorax, pulmonary congestion and edema, hepatomegaly (nutmeg liver) were present in most dogs at autopsy. A few had distended neck veins and peripheral pitting edema. Microscopic examination confirmed the presence of severe passive congestion involving the lungs, liver, kidneys and other organs. The anatomic diagnoses were chronic non-bacterial pericarditis with effusion; passive hyperemia of the liver, kidneys and lungs; anasarca.

3. *Physiological data.*

*A. Sequence of changes*

Placement of an irritative cellophane bag about the heart induced an essentially similar course in all dogs. The duration of life after surgery varied from six to 44 days. With varying degrees of rapidity the dogs developed an enlarged "cardiac" silhouette, tachycardia, venous congestion, ascites, anorexia, weakness, hydrothorax, respiratory difficulty (hyperpnea) and, occasionally, peripheral pitting edema. The mean blood pressure and pulse pressure were well maintained until late; one to four days pre-terminally, prostration and circulatory collapse ensued. The sequence of physiological changes seen in two typical dogs (P2 and P4) is recorded in detail in Tables II and III and diagrammatically summarized in Figure 1. The pattern of the alterations may be divided into three temporal phases: (*1*) early, (*2*) late, and (*3*) pre-terminal pericarditis with effusion.

*Pericarditis with effusion, early:* In every dog, the initial change registered after operation was a progressive rise in peripheral venous pressure with a concomitant elevation of central and renal venous pressures. By the third to seventh postoperative day the peripheral venous pressure was definitely above control values (Table IVA). At this time a considerable pericardial effusion was noted on fluoroscopy, and the presence of inflammatory serosanguinous fluid was established by puncture.

No dog exhibited a significant alteration in resting renal plasma flow or glomerular filtration rate at this time (Table IVA). However, at the time that the venous pressure began to rise, sodium clearances suggested an impaired capacity of the kidneys to dispose of a sodium load (Table V). Concurrent studies revealed that no dog had as yet developed a measurable alteration in plasma volume or thiocyanate space (Table IVA). Early in pericarditis with effusion, there was neither hyper- nor hypovolemia. Resting cardiac output and arteriovenous oxygen difference also remained at control values.

*Pericarditis with effusion, late:* With progression of the circulatory changes, the gradual rise in peripheral and central venous pressures continued (Table IVB). Gross anasarca became evident. The thiocyanate space was significantly increased in every dog (Table IVB). Two dogs (P2, P3) exhibited an increased plasma volume, with an accompanying decrease in hematocrit and plasma protein concentration. In one animal (Z102) there was no evidence of hypervolemia and hydremia; the plasma volume remained at control levels throughout (Table IVB). Dog P4 had normovolemia until the infusion of hypertonic saline for sodium clearance (Tables III and IV). During this late phase of pericarditis with effusion, the resting renal plasma flow and glomerular filtration rate continued at control levels. No depression of resting cardiac output was recorded. However, the three dogs studied (P2, P4, P5) had increased arteriovenous oxygen differences. A moderate fall in systolic and mean arterial blood pressure and in pulse pressure was noted (Tables II and III).

*Pericarditis with effusion, pre-terminal:* This phase was ushered in by circulatory collapse, moderate to severe. The pulse became weak, rapid and thready. The arterial blood pressure was considerably reduced (*e.g.*, P2, Table II) or altogether unrecordable. The animals were prostrate,

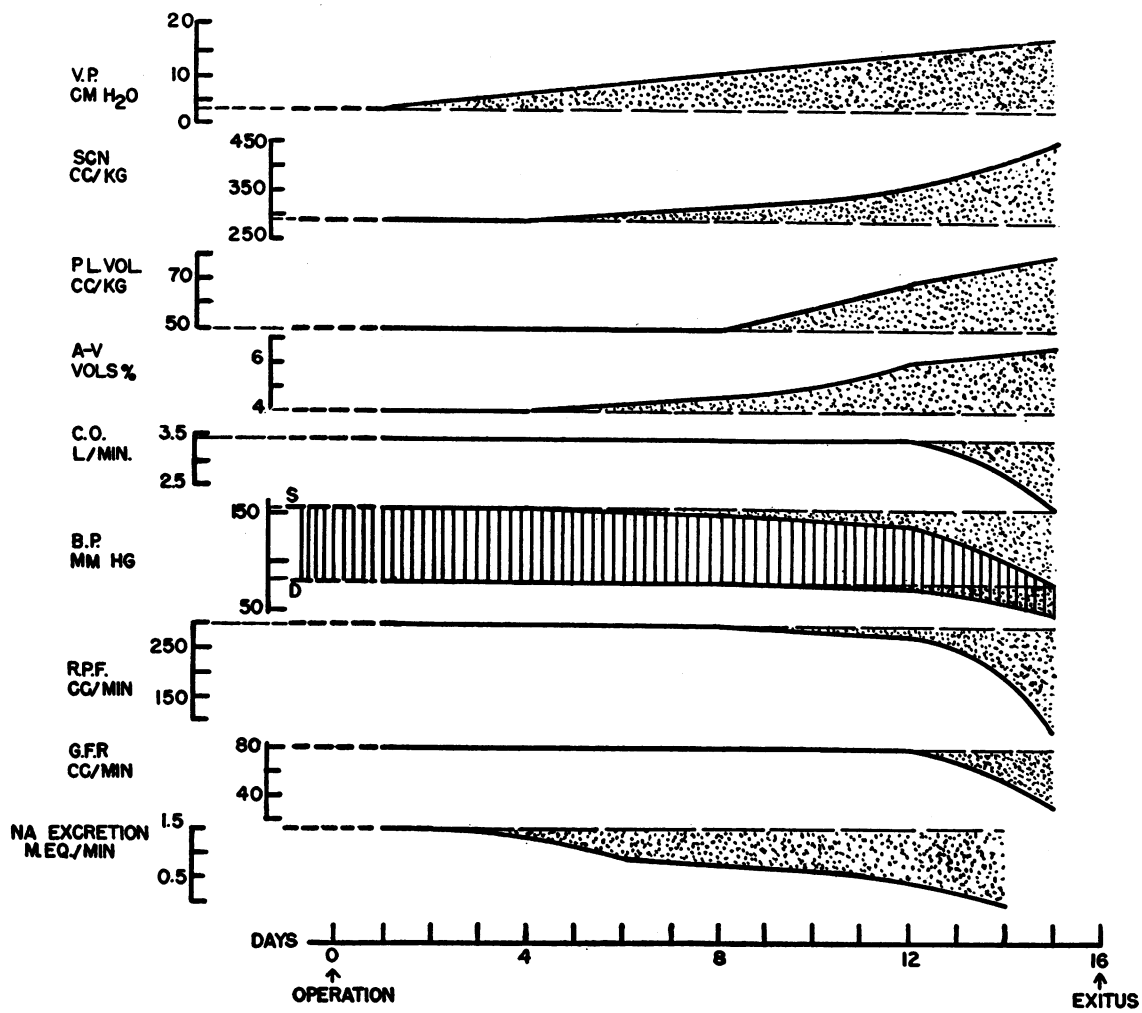


FIG. 1. SEQUENCE OF PHYSIOLOGICAL CHANGES IN CHRONIC EXPERIMENTAL PERICARDITIS WITH EFFUSION: SEMI-DIAGRAMMATIC SUMMARY OF DATA OBTAINED ON NINE DOGS (CF. TABLES I–VI)

*V.P.*, peripheral venous pressure; *SCN*, thiocyanate space; *PL. VOL.*, plasma volume; *A–V*, arteriovenous oxygen difference in volumes per cent of $O_2$; *C.O.*, cardiac output; *B.P.*, blood pressure (*S*, systolic and *D*, diastolic); *R.P.F.*, renal plasma flow; *G.F.R.*, glomerular filtration rate; *Na excretion*, sodium excretory rate in milliequivalents of sodium per minute, in the face of an intravenous hypertonic saline load; ↑ *OPERATION*, day of operative placement of irritative cellophane bag about the heart, between visceral and parietal pericardial layers. Abscissa represents days postoperative to death (↑ *EXITUS*). Discussed in text.

had considerable respiratory distress (hyperpnea) and were obviously *in extremis*. Except for dog P2 (Table II), this phase lasted no longer than 24 hours. The peripheral and central venous pressure and the intrapericardial pressure were markedly elevated. The effective filling pressure of the right atrium was severely impaired. Cardiac output determination was done in one dog at this time. A moderate reduction in resting cardiac output was recorded, with an increased arteriovenous oxygen difference (P2, Table II). In two dogs (P2, P4—Tables II and III) the resting renal plasma flow and glomerular filtration rate were significantly decreased, with an increased filtration fraction. Sodium clearances revealed marked impairment of renal ability to dispose of an intravenous sodium load (Table VI). Data on weight, thiocyanate space and venous pressure 24 hours after this sodium clearance revealed marked retention of the administered saline solu-

TABLE IV

*Changes in venous pressure, plasma volume, thiocyanate space, renal clearances in early and late pericarditis with effusion*

| Dog No. | Time of observation, days post-operative | Time of death, days post-operative | V.P. change* | Plasma vol. change | Thiocyanate space change | GFR change* | RPF change* |
|---|---|---|---|---|---|---|---|
| | | | A. Early Changes | | | | |
| | | | *cm. $H_2O$* | *cc./kg.* | *cc./kg.* | *cc./min.* | *cc./min.* |
| P2 | 3 | 21 | + 3 | + 8 | − 15 | −10 | + 54 |
| P4 | 4 | 11 | +10 | − 2 | — | + 2 | − 2 |
| P5 | 4 | 6 | + 6 | −11 | − 21 | +11 | + 17 |
| Z102 | 6 | 11 | + 4 | 0 | — | − 8 | + 1 |
| P3 | 4 | 11 | + 5 | — | — | − 1 | + 24 |
| P6 | 4 | 4 | + 5 | + 2 | — | + 2 | 0 |
| | | | B. Late Changes | | | | |
| P2 | 16 | 21 | + 9 | +25 | + 47 | −15‡ | − 9‡ |
| P4 | 11 | 11 | +14 | +18† | +306† | −17 | −140 |
| P5 | 5 | 6 | + 9 | — | — | +11 | + 17 |
| Z102 | 9 | 11 | +12 | 0 | +182 | + 1 | − 5 |
| P3 | 7 | 11 | +13 | +22 | +116 | − 3 | − 35 |
| P6 | — | 4 | — | — | — | — | — |

* For symbols see Table I.

† Marked changes are due to the retention of saline administered intravenously on the previous day. Prior to this infusion the thiocyanate space was elevated only 7 cc./kg. above control levels. See text.

‡ Four days later, this dog exhibited markedly depressed renal clearance values. See text.

TABLE V

*Sodium clearance studies—early pericarditis with effusion**

| Dog No. | Status | RPF | Plasma Na | GFR | Na filtered | U.F. corrected† | Urine Na | Na excreted | Na reabsorbed | % Na reabsorbed | % Na excreted | $H_2O$ reabsorbed | M.eq. Na reabsorbed per 1000 cc. $H_2O$ reabsorbed |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *cc./min.* | *m.eq./cc.* | *cc./min.* | *m.eq./min.* | *cc./min.* | *m.eq./cc.* | *m.eq./min.* | *m.eq./min.* | | | *cc./min.* | |
| P6 | Control—infusion of 800 cc. 2.5% saline | 428 | .166 | 85 | 14.10 | 10.5 | .123 | 1.68 | 12.42 | 88.0 | 12.0 | 74.5 | 166 |
| | | 335 | .166 | 84 | 13.94 | 8.3 | .107 | 1.28 | 12.66 | 90.9 | 9.1 | 75.7 | 167 |
| | | 346 | .188 | 81 | 15.23 | 8.6 | .106 | 1.33 | 13.90 | 91.3 | 8.7 | 72.4 | 192 |
| P6 | Control—infusion of 855 cc. 2.5% saline | 266 | .178 | 90 | 16.02 | 4.1 | .157 | 1.05 | 14.97 | 93.4 | 6.6 | 85.9 | 174 |
| | | 248 | .182 | 101 | 18.31 | 4.7 | .167 | 1.17 | 17.14 | 93.5 | 6.5 | 96.3 | 178 |
| | | 257 | .180 | 93 | 16.74 | 6.1 | .169 | 1.45 | 15.29 | 91.3 | 8.7 | 86.9 | 176 |
| | Mean of six control periods | 313 | .177 | 89 | 15.76 | 7.1 | .138 | 1.39 | 14.37 | 91.2 | 8.8 | 81.9 | 175 |
| | Range | 248–428 | .166–.188 | 81–101 | 13.94–18.31 | 4.1–10.5 | .106–.169 | 1.05–1.68 | 12.42–17.14 | 88.0–93.5 | 6.5–12.0 | 72.4–96.3 | 166–192 |
| P6 | Early pericarditis with effusion—1480 cc. 2.5% saline infusion | 347 | .188 | 118 | 22.19 | 6.8 | .109 | .98 | 21.21 | 95.7 | 4.3 | 111.2 | 191 |
| | | 288 | .190 | 70 | 13.30 | 5.8 | .095 | .81 | 12.49 | 93.9 | 6.1 | 64.2 | 195 |
| | | 258 | .188 | 68 | 12.69 | 6.1 | .101 | .79 | 11.90 | 93.8 | 6.2 | 61.9 | 191 |
| | Mean | 298 | .189 | 85 | 16.06 | 6.2 | .102 | .86 | 15.20 | 94.6 | 5.4 | 78.8 | 193 |
| | Range | 258–347 | .188–.190 | 68–118 | 12.69–22.19 | 5.8–6.8 | .095–.109 | .79–.98 | 11.90–21.21 | 93.8–95.7 | 4.3–6.2 | 61.9–111.2 | 191–195 |

* Venous pressure at this time was elevated 5 cm. $H_2O$ to a level of 13 cm. $H_2O$.

† U.F. is the urine flow; the correction is for the amount of water added to the urine during washing of the bladder. Other symbols as in previous tables.

tion (Table III). This infusion apparently accelerated exitus of this dog. A similar response to intravenous saline solution has been noted previously in human constrictive pericarditis, but no renal clearances were done in these patients (33).

### *B. Alterations in individual functions*

*Peripheral venous pressure:* As pericarditis with effusion developed and progressed to tamponade, the peripheral venous pressure progressively rose. This rise in venous pressure was the

TABLE VI

*Sodium clearance studies—late pericarditis with effusion*

| Dog No. | Status | RPF | Plasma Na | GFR | Na filtered | U.F. corrected* | Urine Na | Na excreted | Na reabsorbed | % Na reabsorbed | % Na excreted | $H_2O$ reabsorbed | M.eq. Na reabsorbed per 1000 cc. $H_2O$ reabsorbed |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *cc./min.* | *m.eq./cc.* | *cc./min.* | *m.eq./min.* | *cc./min.* | *m.eq./cc.* | *m.eq./min.* | *m.eq./min.* | | | *cc./min.* | |
| P4 | Control—hydration with 0.9% saline I-V, 850 cc. | 314 | .158 | 74 | 11.70 | 2.4 | .071 | .31 | 11.39 | 97.3 | 2.7 | 71.6 | 160 |
| | | 336 | .158 | 76 | 12.00 | 2.4 | .103 | .36 | 11.64 | 97.0 | 3.0 | 73.6 | 158 |
| | | 226 | .159 | 52 | 8.28 | 1.5 | .068 | .23 | 8.05 | 97.3 | 2.7 | 50.5 | 159 |
| | Mean | 292 | .158 | 67 | 10.59 | 2.1 | .081 | .30 | 10.29 | 97.2 | 2.8 | 64.9 | 159 |
| P4 | Late pericarditis—hydration with 2300 cc. 0.9% saline, 1000 cc. 2.5% mannitol, 300 cc. 5% saline I-V† | 113 | .139 | 44 | 6.08 | 2.0 | .000 | .00 | 6.08 | 99.9+ | <0.1 | 42.0 | 146 |
| | | 135 | .140 | 59 | 8.26 | 2.5 | .000 | .00 | 8.26 | 99.9+ | <0.1 | 56.5 | 146 |
| | | 151 | .150 | 53 | 7.95 | 1.3 | .001 | <.01 | <7.95 | 99.9+ | <0.1 | 51.7 | 154 |
| | | 158 | .154 | 67 | 10.32 | 1.3 | .002 | .01 | 10.21 | 99.9+ | <0.1 | 65.7 | 156 |
| | Mean | 139 | .146 | 56 | 8.18 | 1.8 | .001 | .005 | 8.175 | 99.9+ | <0.1 | 54.2 | 150 |

* U.F. is the urine flow; the correction is for the amount of water added to the urine during washing of the bladder. Other symbols as in previous tables.

† Great difficulty was encountered in obtaining diuresis; see text.

first change recorded in these dogs. From usual preoperative values of 3–5 cm. $H_2O$, peripheral venous pressure increased to a pre-terminal level as high as 17–18 cm. (Figure 1 and Tables II–IV).

*Central venous, renal venous and intrapericardial pressures:* Early in pericarditis with effusion, when there was an increment of 3–6 cm. $H_2O$ in peripheral venous pressure, renal venous pressure exhibited a similar increase (dog P8). Two dogs (P4 and P9) catheterized pre-terminally one day prior to death, had peripheral venous pressures of 17 and 16 cm. $H_2O$ (control: 3 and 6 cm.) respectively. The renal venous pressures were 26 and 25 cm. $H_2O$ (control: 9 and 11 cm.) respectively. The renal venous pressure increments are probably the combined effect of generalized venous pressure elevation and of the increased intra-abdominal pressure (ascites) acting on the renal vein (34–36). The right atrial pressure (P9) was 11–13 cm. $H_2O$ (control: 2–4 cm.); the intrapericardial pressure was 11 cm. $H_2O$. Hence the effective filling pressure of the right atrium was 0–2 cm. $H_2O$. This dog had pulsus paradoxus by record (37). In P4, the intrapericardial pressure immediately postmortem was 14 cm. $H_2O$.

*Plasma volume and thiocyanate space:* There were no significant changes in plasma volume or thiocyanate space until the late phase of pericarditis with effusion (Table IV). At that time, every dog had a grossly elevated thiocyanate space (Figure 1). Two (P2, P3) had an increased plasma volume. Gross anasarca was readily identifiable at this time.

*Hematocrit and plasma total protein:* In the early phase of pericarditis with effusion these values were normal or only slightly reduced. As the process progressed, there was a significant further decrease in both these values. During the late phase, the decrements were in the range $-7$ to $-23\%$, and $-0.4$ to $-1.5$ gms.% for hematocrit and plasma total protein respectively. This is correlative evidence for the development of hypervolemia and hydremia.

*Weight:* There were no significant changes in weight, except for the preterminal increase in P4, due to retention of administered saline. The marked anorexia supervening some days prior to death apparently accounted for the stationary weight in the face of progressive gross fluid retention.

*Cardiac output, arteriovenous oxygen difference, oxygen consumption:* The resting cardiac output remained at control levels until pre-terminally. However, both oxygen consumption and arteriovenous oxygen difference increased during the late phase of pericarditis with effusion. The increased oxygen consumption was associated with hyperpnea, probably due to pulmonary venous congestion (38). Hence in relation to level of work performed by the animal in this hyperpneic condition, a resting cardiac output at control levels is not "normal." The abnormal nature of this cardiac response is confirmed by the increased arteriovenous oxygen difference (9).

The last cardiac output recorded in dog P2 was reduced approximately 25% compared with previous values (Table II). This value may represent a significant preterminal depression of resting cardiac output below control levels.

*Heart rate:* Tachycardiac developed 24–48 hours postoperatively and persisted. With preterminal circulatory collapse, the pulse became extremely rapid (Tables II and III).

*Arterial blood pressure:* The blood pressure and pulse pressure were well maintained until preterminally (Tables II and III, Figure 1). A shock-like state supervened prior to death. Dog P4 was unique in exhibiting a blood pressure of 80/50 mm. Hg three days prior to death (Table II). Apparently this state of moderately severe circulatory collapse persisted thereafter until the dog succumbed.

*Renal clearances:* Renal plasma flow, glomerular filtration rate, and filtration fraction remained at control levels until very late or pre-terminally (Tables II–IV, Figure 1). Data were obtained 24 hours prior to death on both P2 and P4. The former exhibited marked depression of both renal plasma flow and glomerular filtration rate, with an increased filtration fraction. Blood pressure was reduced to about 80/50 at this time; venous pressure was considerably elevated; cardiac output was depressed below control levels (Table II). P4 exhibited a less marked but nevertheless significant reduction in renal plasma flow, with a slightly lowered glomerular filtration rate and an elevated filtration fraction.

*Sodium excretion:* Data on sodium clearance suggest moderate impairment of renal sodium excretory capacity early in pericarditis with effusion (Table V). This finding was recorded on the initial day of definitive venous pressure elevation, and in the presence of a normal glomerular filtration rate, renal plasma flow and blood pressure. Compared with control determinations, a greater load of intravenous hypertonic saline was given. Plasma sodium levels were considerably higher than in the preoperative control clearances. Therefore the amount of sodium presented to the renal tubules per minute (Na filtered in milliequivalents per minute, Table V) was greater. Nevertheless both the actual amount of sodium excreted per minute and the per cent excretion of filtered sodium were reduced. There was increased reabsorption (in both per cent and milliequivalents per minute) of filtered sodium by the renal tubules.

These data suggesting moderately impaired sodium excretory capacity early in pericarditis with effusion were recorded four days postoperatively. This dog (P6) had a peripheral venous pressure elevation of 5 cm. $H_2O$ at that time (Table IV). There were no other significant observed changes.

In another dog, P7, sodium clearances were done three days postoperatively, at a time when no rise in venous pressure or other significant change had yet been recorded. These sodium clearance values were in essential agreement with control data. Subsequently this dog exhibited a progressive rise in venous pressure, followed by development of anasarca. It was not possible to do further sodium clearances.

Sodium clearance studies on P4 24 hours prior to death revealed marked impairment of sodium excretory capacity. Venous pressure was considerably elevated at this time. Renal plasma flow was markedly decreased, glomerular filtration rate was slightly reduced. Cardiac output and arterial blood pressure, determined a few hours before, were normal. The arteriovenous oxygen difference was increased. Under these circumstances great difficulty was encountered in obtaining diuresis for renal clearance. Despite a very large load of intravenous hypertonic saline, high plasma sodium levels, and only slightly depressed glomerular filtration rate, the sodium excretory rate was practically nil (Table VI). Almost 100% of the sodium filtered at the glomerulus was reabsorbed by the tubules.

*Effect of pericardiocentesis:* By the 13th postoperative day, dog P2 had a considerable elevation of venous pressure, gross anasarca, marked weakness, anorexia, respiratory distress. The animal appeared to be *in extremis.* At this point, relief of pericardial tamponade was accomplished by withdrawal of about 150–200 cc. of serosanguinous fluid (Table II). The venous pressure immediately fell 6 cm. $H_2O$ to a level of 8 cm. (39–50). The respiratory rate declined from 36 to 24 per minute, apparently due to relief of pulmonary venous congestion (38). The blood pressure rose to 145/80 mm. Hg. The dog's downhill course was temporarily arrested; duration of life was apparently prolonged (Table II). However, the

venous pressure rapidly returned to pre-pericardiocentesis levels; 24 hours after the tap it was again 14 cm. $H_2O$. Soon thereafter, pre-terminal circulatory collapse ensued.

*Effect of exertion and excitement on cardiac output:* On several occasions during the preoperative control periods an opportunity was afforded to record the effect of inadvertent psychic stimulation on cardiac output. A three- to five-fold increase in cardiac output was invariably noted. During the late phase of pericarditis with effusion in dog P2, the resting state was temporarily disrupted in the course of a cardiac output determination. The data revealed no significant increase in output during this brief period of excitement and exertion.

## DISCUSSION

Placement of an irritative cellophane bag about the heart, between the parietal and visceral layers of the pericardium, provokes a chronic pericarditis with effusion. As fluid accumulates, intrapericardial pressure becomes increasingly elevated. The effusion progresses to tamponade. These events in turn catalyze a series of interdependent changes in cardiodynamics and renal function. An elevation in venous pressure is the earliest recorded response to rising intrapericardial pressure, as observed by Cohnheim (39), Starling (40), Kuno (41, 42), Katz and Gauchat (37), Beck and associates (43, 44) and Fineberg (45) in acute experiments, and by Fletcher (46), Warren and his associates (47, 48) and others (49, 50) in man. Our data, too, indicate that the venous pressure rise occurs prior to the development of measurable hypervolemia; this confirms the interrelationship between venous and intrapericardial pressures in acute and chronic pericardial tamponade. Even in chronic tamponade, hypervolemia would appear to play only a secondary role in contributing to the venous pressure rise. It has been suggested that the rise in venous pressure in pericardial tamponade is accomplished by a shift of blood from the smaller vessels (arterioles and venules) and possibly by an increase in venomotor tone (1, 2, 47, 48).

The venous pressure rise in response to pericardial effusion operates to support the effective filling pressure of the right atrium. Resting minute volume of the heart is maintained by a combination of elevated venous pressure and tachycardia. This compensatory mechanism is not limitless, even at rest. When a critical level of intrapericardial pressure of between 10 to 15 cm. of water is reached, effective filling pressure of the right atrium is markedly reduced (49, 50). Resting cardiac output drops and arterial blood pressure falls. This ushers in the phase of preterminal circulatory collapse.

These facts are pertinent for the elucidation of the mechanism of edema formation in pericarditis with tamponade. The venous pressure elevation precedes rather than follows an increase in extravascular fluid (3, 51). It would seem that the increase in intrapericardial pressure, venous pressure and extravascular fluid volume follow one another in close order. This sequence implies fluid loss from the vascular tree into the tissues and consequent hemoconcentration and hypervolemia. However, in actuality the process of chronic edema formation is not a deviation of extracellular fluid from intravascular to extravascular compartments. The *total* extracellular fluid increases. There is fluid retention which effectively maintains the circulating plasma volume and may eventuate in hypervolemia.

Our data show that fluid retention occurs at a time when the resting cardiac output, renal plasma flow, glomerular filtration rate and blood pressure are at control levels. Only the venous pressure is elevated.

Blake and his colleagues (52) have recently shown in acute experiments on anesthetized dogs that unilateral elevation of the renal venous pressure causes a decreased salt and water excretion by the homolateral kidney. This occurs at levels of increased venous pressure that do not cause a depression of renal plasma flow and glomerular filtration rate. It was concluded that a rise in venous pressure somehow effects increased tubular reabsorption of sodium and water.

In our dogs pericardial tamponade elicited a generalized elevation of venous pressure and later a localized intra-abdominal venous pressure rise due to ascites. The resultant renal venous pressures were in the range induced by Blake and colleagues (52). Our data on sodium clearances obtained early in the course of pericarditis with effusion correspond well with the findings of these investigators. They clarify how elevated vascular

hydrostatic pressure may lead to edema formation and fluid retention with resting cardiac output and renal clearances at control levels, and without the development of hypovolemia and hemoconcentration. It would appear that in our animals venous pressure elevation, increased renal tubular sodium and water reabsorption, and edema formation develop and proceed in close temporal interrelationship. Thus, fluid retention by the kidney preserves plasma volume, although edema fluid is being extravasated from the blood vascular space.

It is not to be inferred that this is the sole mechanism for salt and water retention in pericarditis with effusion. Thus it has been shown that several pathophysiologic alterations lead to decreased renal plasma flow and glomerular filtration rate, *e.g.,* reduced cardiac output (4, 6), lowered blood pressure (53), marked renal venous pressure rise (5, 52). The resultant abnormal kidney function is associated with sodium retention, apparently due to both decreased glomerular filtration rate (decreased presentation of sodium to the renal tubules for reabsorption) and increased per cent reabsorption of filtered sodium (4–7, 10). In the late or pre-terminal phase of pericarditis with effusion all these mechanisms may operate to accelerate fluid retention.

Recent work has also shown that in congestive heart failure, changes in kidney function result from inability to increase cardiac output to meet the needs of exercise. A disproportionate reduction in renal blood flow and a further rise in renal venous pressure occur with consequent sodium retention (4, 5, 7).

Our survey of the literature failed to reveal any data on cardiac output and renal clearances during exercise in pericardial tamponade. In anesthetized dogs with acute tamponade, Landis and his associates (8) noted a fall in central venous pressure during exercise. This was attributed to decreased mean intrapericardial pressure resulting from deep inspiration (hyperpnea of exercise). Marked tachycardia also supervened. It was surmised that ". . . once past the mechanical barrier, blood entered the relatively normal heart and was expelled efficiently" (8). Presumably, then, cardiac output was able to increase and meet the needs of exercise under the conditions of this experiment.

Our data on intact unanesthetized dogs with progressive severe chronic pericardial tamponade suggest that their capacity for increased cardiac output during exertion is severely limited. Hence it would appear that during activity these animals exhibit the pathological alterations in renal plasma flow, glomerular filtration rate and sodium excretion observed in cases of congestive heart failure. These alterations constitute a further possible mechanism augmenting fluid accumulation in pericarditis with tamponade.

In brief, it is evident that both early and late in pericarditis with effusion, derangements in cardiodynamics occur which lead to fluid accumulation because of their effects on the kidney.

Our findings bring into focus the essential differences and similarities between congestive heart failure and pericarditis with tamponade. In heart failure, the ability to increase cardiac output to meet increased demands is limited because of intrinsic cardiac disease. In chronic pericarditis with tamponade, the myocardium is adequate. Increased intrapericardial pressure induces a venous pressure rise. In both heart failure and pericardial tamponade, once these initial pathophysiologic alterations come into play, essentially similar mechanisms operate to produce extracellular fluid accumulation. Thus in both conditions, during both rest and exercise, "backward failure" mechanisms may supplement "forward failure" mechanisms. Both lead to renal retention of sodium and water.

## SUMMARY AND CONCLUSIONS

The interdependent cardiodynamic and renal mechanisms producing fluid retention in pericarditis with effusion have been studied. In pericarditis with tamponade peripheral and central venous pressure rises with increased intrapericardial pressure. This rise occurs without hypervolemia. It supports right atrial effective filling pressure and helps to preserve cardiac output.

Increased hydrostatic pressure induces extravasation of fluid from the vascular tree (edema formation). Simultaneously, increased renal venous pressure may lead to decreased sodium and water excretion (increased tubular reabsorption) in the absence of decreased resting cardiac output, renal plasma flow, glomerular filtration rate and arterial blood pressure. This prevents hemoconcentration and hypovolemia despite progressive edema formation. There is an overall retention

of salt and water, and an increase in total extracellular fluid. Eventually anasarca and hypervolemia develop.

The ability of the heart with tamponade to increase its output to meet the needs of activity is apparently limited. With exercise, inadequacy of cardiac output may bring into play "forward failure" mechanisms (*e.g.*, inordinately decreased renal plasma flow and glomerular filtration rate) which contribute to the salt and water retention.

Progressive tamponade leads to further rises in venous pressure. Pre-terminally a critical level is reached; this mechanism no longer suffices to maintain adequate resting cardiac output. Cardiac output is reduced, arterial blood pressure falls. Both renal plasma flow and glomerular filtration rate decrease precipitously; sodium excretory capacity is further severely impaired. These several mechanisms responsible for reduced renal salt and water excretion now operate synergistically to accelerate fluid retention and aggravate circulatory embarrassment.

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